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*Original article (short paper)*

## **Exercise and cognitive functions in Parkinson's disease: Gender differences and disease severity**

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**Abstract**—This study investigated the effect of a multimodal exercise program on executive functions and memory in people with Parkinson's disease, taking into account disease severity and gender. Twenty-three patients with Parkinson's disease (PD) were evaluated before and after a 6-month exercise program to improve executive functions and memory. We observed the effects of the intervention on executive functions (ability to abstract:  $p = .01$ ), immediate memory ( $p = .04$ ) and declarative episodic memory ( $p < .001$ ). Women showed higher scores on declarative episodic memory ( $p = .03$ ) than men, however there was no interaction between gender and the intervention. Regardless of sex and disease severity, these preliminary results indicate that the multimodal exercise seems to be effective in improving cognitive functions in patients with PD, suggesting that this program can be indicated as a preventive strategy to mitigate progressive cognitive deficits in the later stages of the disease.

**Keywords:** exercise, executive functions, memory, Parkinson's disease

**Resumo**—“Exercício físico e funções cognitivas na doença de Parkinson: Diferença entre sexos e severidade da doença.” Este estudo investigou o efeito de um programa de exercícios multimodal nas funções executivas e na memória de pessoas com doença de Parkinson (DP), considerando gênero e severidade da doença. As funções executivas e a memória de 23 pacientes com DP foram avaliadas antes e após 6-meses de participação no programa de exercícios. Foi observado efeito da intervenção nas funções executivas (habilidade de abstração:  $p = 0,01$ ), memória imediata ( $p = 0,04$ ) e memória declarativa episódica ( $p < 0,001$ ). As mulheres mostraram maior pontuação na memória declarativa episódica ( $p = 0,03$ ) que os homens, entretanto não foi observada interação entre gênero e intervenção. Estes resultados preliminares indicam que o exercício multimodal parece eficaz em melhorar as funções cognitivas em pacientes com DP, independente do gênero e da severidade da doença, sugerindo que este programa pode ser indicado como estratégia preventiva para atenuar a progressão dos déficits cognitivos nos estágios mais avançados da doença.

**Palavras-chave:** exercício físico, funções executivas, memória, doença de Parkinson

**Resumen**—“El ejercicio y funciones cognitivas en la enfermedad de Parkinson: Diferencias entre género y la gravedad de la enfermedad.” Este estudio investigó el efecto del ejercicio multimodal en las funciones ejecutivas y la memoria en la enfermedad de Parkinson (EP), teniendo en cuenta el género y la gravedad de la enfermedad. Funciones ejecutivas y memoria de 23-pacientes con EP fueron evaluadas antes y después de 6-meses de participación en el programa. El efecto de la intervención fue observado en las funciones ejecutivas (capacidad de abstracción:  $p = 0,01$ ), memoria inmediata ( $p = 0,04$ ) y memoria declarativa episódica ( $p < 0,001$ ). Las mujeres mostraron puntuaciones más altas en memoria declarativa episódica ( $p = 0,03$ ) que los hombres, aunque no hubo interacción entre género e intervención. Estos resultados preliminares indican que el ejercicio multimodal parece ser eficaz en la mejora de la función cognitiva en pacientes con EP, independiente del género y de la gravedad de la enfermedad, lo que sugiere que este programa puede ser indicado como una estrategia preventiva para atenuar la progresión de los déficits cognitivos en las etapas tardías de la enfermedad.

**Palabras clave:** ejercicio, funciones ejecutivas, memoria, enfermedad de Parkinson

## Introduction

Decay of cognition may be manifested by early executive impairment (Stella *et al.*, 2007). Several studies have demonstrated that a substantial portion of patients with Parkinson's disease (PD) have cognitive deficits even in the early course of disease (Aarsland *et al.*, 2010; Caviness *et al.*, 2007; Janvin, Larsen, Aarsland, & Hugdahl, 2006). Among cognitive domains, memory impairment is the most common deficit, followed by visual-spatial and executive function impairment, but, in some cases, the impairment occurs in multiple cognitive domains (Aarsland *et al.*, 2010).

Regular exercises associated with medical therapy have been effective in providing the quality of life (Hirayama, Gobbi, Gobbi, & Stella, 2008; White, Wagenaar, & Ellis, 2006), the components of physical capacity (Hirsch, Toole, Maitland, & Rider, 2003; Skidmore, Patterson, Shulman, Sorkin, & Macko, 2008); the functional mobility (Frazzitta, Maestri, Uccellini, Bertotti, & Abelli, 2009; Gobbi, Barbieri, Vitorio, Pereira, & Teixeira-Arroyo, 2011, Pereira *et al.*, 2012), and the spatial-temporal parameters of gait (Scandalis, Bosak, Berliner, Heiman, & Wells, 2001; Vítório *et al.*, 2011). However, there are few studies about the effect of exercise on cognitive functions in patients with PD.

Tanaka *et al.* (2009) found significant improvements in executive functions in PD patients after a six-month participation in an aerobic exercise program. However, the effect of this exercise program on patients' memory has not been investigated. On the other hand, four months of participation in two different exercises programs or four months in a program with non-motor activities were equally effective in improving memory and symptoms of stress in patients with PD (Gobbi *et al.*, 2013). However, the authors did not investigate the responses for executive functions and memory after exercise practice in the early and moderate stages of PD.

Studies have shown that, as occurs with motor impairment, patients in the advanced stages of the disease have greater impairment of cognitive performance than their peers in the early stages of PD (Bronnick, Emre, Lane, Tekin, & Aarsland, 2007; Chaudhuri, Healy, & Schapira, 2006; Weintraub, Moberg, Duda, Katz, & Stern, 2004). A recent meta-analysis showed that there is a gap in the literature regarding the effects of exercise on patients at different stages of PD (Goodwin, Richards, Taylor, Taylor, & Campbell, 2008). This is of particular importance given the deteriorating effects of this disease. Thus, it is important to know whether patients in the early stages respond similarly to exercise and the optimal exercise intervention for each stage of progression of PD.

Parkinson's disease has a higher incidence in men than in women (Bower, Maraganore, McDonnell, & Rocca, 2000). However, other differences between genders, like the different responses from exercise are not known. Moreover, there are few studies that consider the effect of gender on cognitive functions in adults and the elderly and even fewer on people with PD. The typical signs of PD are present in both males and females. However, motor symptoms associated with each gender are different (Scott, Borgman, Engler, Johnel, &

Aquilonius, 2000). The magnitude of the effect of fitness on cognition is conditioned by many factors, including the length of the fitness-training intervention, the type of the intervention, the duration of training sessions, and gender (Colcombe & Kramer, 2003). Prospective studies have shown that both genders respond positively to exercise with respect to their cognitive function (Taaffe *et al.*, 2008; Yaffe, Barnes, Nevitt, Lui, & Covinsky, 2001; Weuve *et al.*, 2004). However, men and women between 32 and 62 years old show differences in performance on cognitive tests (Cournot *et al.*, 2006). Males are over-represented in most studies of exercise intervention in PD, and the results are generalized (Goodwin, Richards, Taylor, Taylor, & Campbell, 2008). This raises the question of whether these interventions are acceptable for women with PD and whether responses to the same exercise protocol are the same for men and women.

Based on these assumptions, the aim of this study was to investigate the effect of a multimodal exercise program on executive functions and memory (cognitive domains) in people with PD according to disease severity and gender.

When the first symptoms of PD are detected, approximately 80% of dopaminergic cells have already been damaged, which gradually worsens with disease progression (Olanow, Stern, & Sethi, 2009). Although the dopaminergic neurons are highly responsive to exercise (Fox *et al.*, 2006), the drastic decrease of dopaminergic neurons in the late stages of PD can cause a decrease in neuroplasticity in response to exercise. Therefore, we hypothesized that the effects of exercise are most evident in patients in the early stages of the disease.

Sex hormone levels seem to be related to some cognitive abilities, particularly memory, and the dopaminergic system participates in the mediation of memory. Relationships between dopamine availability in the caudate, putamen and in executive motor functioning were observed in women, but not in men (Mozley, Gur, Mozley, & Gur, 2001). It is believed that a diversified exercise program could promote positive effects for men and women, although the magnitude of that gain may be different between genders.

## Method

### *Participants and procedures*

The study protocol was approved by the Research Ethics Committee at the São Paulo State University, Rio Claro campus (# 1058/2007). Patients gave their written informed consent, were screened and underwent evaluation by an expert psychiatrist (FS). The criteria for participation in this study were: i) to present equal age or greater than to 50 years old; ii) current clinical diagnosis for idiopathic PD; iii) scoring between stages 1 and 3 on the Hoehn and Yahr (H&Y) scale; (Goetz *et al.*, 2004; Hoehn & Yahr, 1967) iv) no signs of dementia based on results in the Mini Mental Status Examination (MMSE) (Folstein, Folstein, & Mchug, 1975), which was adjusted according to patients' education level for the Brazilian population (Brucki, Nitrini, Caramelli,

Bertolucci, & Okamoto, 2003); v) no signs of other neurological disease associated with PD; vi) not be participating in any other physical activity program.

The patients were recruited through the assistance of physicians (neurologists and psychiatrists) from the city of Rio Claro, São Paulo, Brazil. Thirty-one patients with PD participated in the initial screening. Only one patient did not agree to participate in the exercise program. Then, 30 patients participated in the exercise program, however 4 of them did not complete the diagnosis screening protocol for PD, 1 patient was younger than 50 years old, and 2 have had a stroke episode. The final sample consisted of 23 patients (12 men and 11 women) with idiopathic PD (Table 1). According to the severity of PD, 15 participants were in the early stage of the disease (unilateral disease: scores 1 to 1.5 in H&Y scale, 7 men and 6 women), and 8 participants were in the moderate stage (bilateral disease: scores 2 to 3 score in H&Y scale, 4 men and 4 women). All participants performed the same multimodal exercise program. The exercise program was administered to a group of 10 participants simultaneously, in a 60-minute session, three times a week, for 6 months, under the supervision of at least four physical education professionals at each session. Even in moderate stages of the disease, most of patients with PD are able to exercise (Olanow, Stern, & Sethi, 2009). However, when necessary, adjustments were made in the proposed activities, ensuring the involvement of all participants and the achieving of the established goals.

### Multimodal exercise program

The multimodal exercise program consisted of aerobics activities (moderate intensity) and included different types of activities that simultaneously benefited the components of functional capacity, such as flexibility (stretching), muscular resistance (specific exercises for large muscle groups), motor coordination (rhythmic activities), and balance (recreational motor activities). These components were selected because they seem to be those most affected by PD (Alves, Wentzel-Larsen, Aarsland, & Larsen, 2005; Olanow, Stern, & Sethi, 2009; Wolfson, Judge, Whipple, & King, 1995).

The program was divided into six phases; each phase (1 month- time) included 12 sessions. Each session consisted of five parts (warm-up, pre-exercise stretching, exercise session, cool-down and post exercise stretching). At the end of each phase there was a progressive increase in load intensity and in the complexity of the exercises (Figure 1). Heart rate during the session remained between 60% and 80% of maximum heart rate (220 minus the participant's age in years) (the details of the program can be obtained in Tanaka *et al.*, 2009).

Long-term duration is a differential of our program, since most studies with PD patients apply short-term protocols. The relatively longer duration (6 months) was set mainly to try to rule out: (i) any eventual time constraint on adaptations to the different and progressive phases of the exercise program; and (ii) any learning effect on the performance of neuropsychological post-tests due to exposure to them during the pre-tests.

Table 1. Demographic, clinical and functional characteristics of the groups. Differences between groups at baseline.

Measure		Total ( <i>n</i> =23)	Men(M) ( <i>n</i> =12)	Women(W) ( <i>n</i> =11)	≠ between M and W ( <i>p</i> values)	Early stage of PD (ES) HY 1-1.5 ( <i>n</i> =15)	Moderated stage of PD (MS) HY 2-3 ( <i>n</i> =8)	≠ between ES and MS ( <i>p</i> values)
Age (years)		66.1±8.6	68.9±7.9	63.0±8.6	.09	63.5±7.7	71.0±8.3	.04*
Educational level (years)		7.9±4.5	8.7±5.57	7.0±3.1	.37	8.4±4.4	7.0±5.0	.49
Disease duration time (years)		4.0±3.7	4.8±4.8	3.0±1.6	.26	3.1±1.7	5.6±5.7	.12
H&Y stage (score)		1.6±0.7	2.0±0.8	2.0±0.7	.35	1.1±0.2	2.5±0.5	<.001*
UPDRS I (score)		3.3±2.3	3.6±2.1	2.9±2.5	.21	3.3±2.2	4.0±3.2	.52
UPDRS II (score)		10.1±7.1	12.9±7.6	7.1±5.2	.07	8.6±4.5	16.3±8.8	.01*
UPDRS III (score)		21.4±13.4	26.4±15.9	16.0±7.4	.12	15.3±4.8	31.9±13.8	<.001*
MMSE (score)		25.8±3.8	25.7±3.7	25.9±4.2	.78	26.6±2.6	24.6±4.8	.21
HAD (score)	Anxiety	5.6±3.9	4.8±3.7	6.5±4.1	.99	4.9±3.2	5.6±2.9	.62
	Depression	6.0±4.2	7.6±4.8	4.3±2.9	.04*	6.2±4.0	5.3±5.8	.64
Functional capacities	Flexibility (cm)	49.7±11.8	48.0±15.0	51.6±7.0	.47	52.9±12.4	43.9±8.1	.08
	Coordination (s)	17.8±6.7	20.1±5.9	15.3±7.0	.09	15.8±4.3	21.78.9±	.04*
	Agility (s)	30.2±13.5	31.2±16.5	29.2±9.9	.73	27.2±11.4	35.8±16.0	.14
	Strength (rep)	20.4±6.0	18.2±5.4	22.8±5.9	.06	22.1±4.7	17.3±7.2	.06
	Aerobic resistance (min)	9.8±1.9	9.8±2.2	9.8±1.7	.99	8.9±1.2	11.6±1.8	<.001*

NOTE: Means ± standard deviation of age, educational level, disease duration time, scores of Hoehn and Yahr Scale (H&Y), Unified Parkinson Disease Rating Scale (UPDRS – subscale I, II and III), MiniMental Status Examination (MMSE), Hospital Anxiety and Depression scale (HAD), and the Functional Capacities (AAHPERD). Results for all group, gender and disease stage. Teste *t* Student para amostras independentes (p values). (\*) Variables that presented significant differences between groups at baseline.



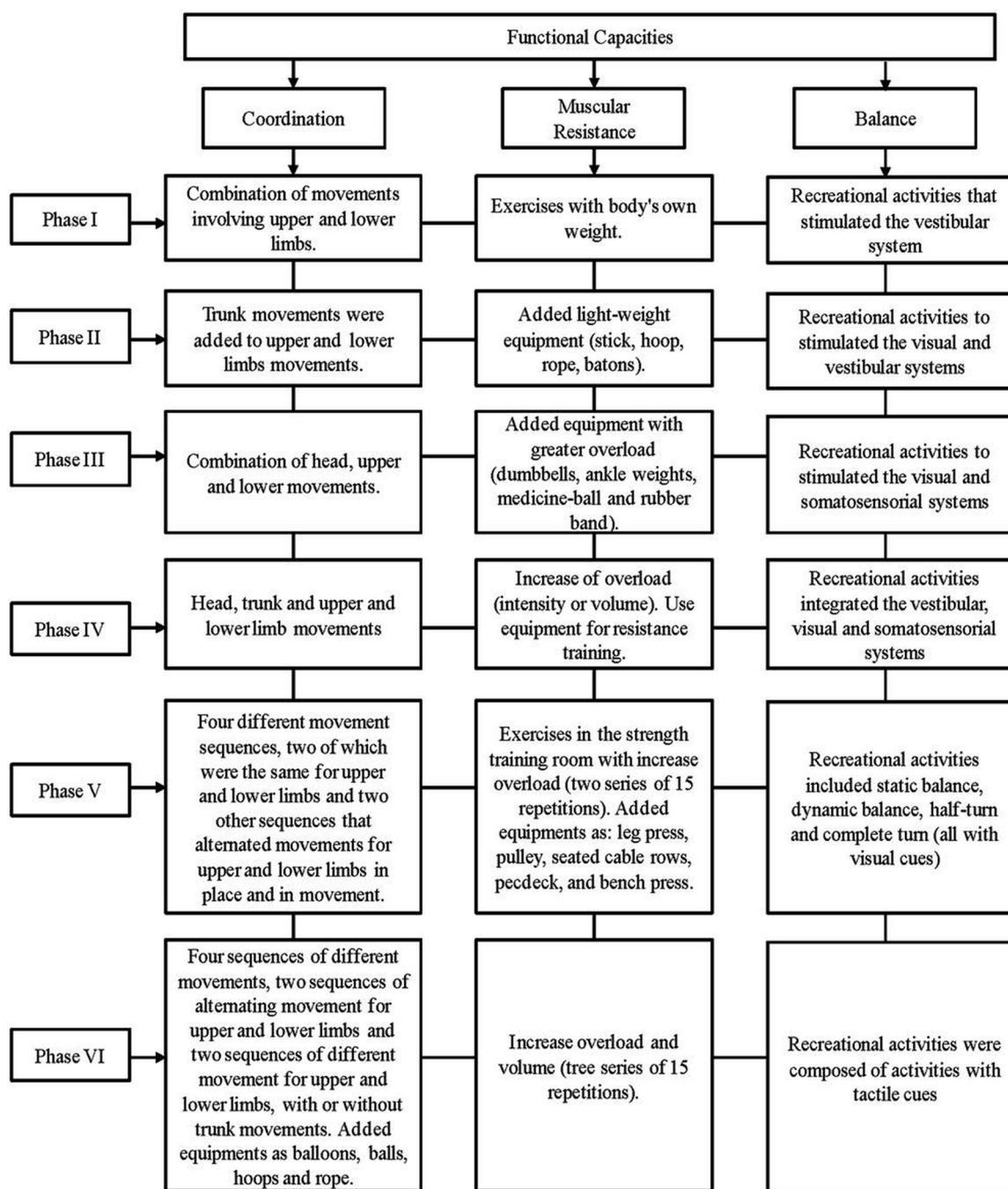


Figure 1. Phases of 6 months of the multimodal exercise protocol with progressive increments on volume, intensity and complexity.

### Evaluations

The patients underwent health screening, clinical evaluation, and an assessment of functional capacity, executive functions and memory before and after the intervention. All participants were evaluated in the “on” state of medication, i.e., 1 hour after participants took the first dose of medication in the morning (dopaminergic replacement therapy with the precursor levodopa or agonists). Medication remained unchanged for all participants during the period of involvement in the study. In the clinical evaluation, information from participants was obtained regarding the following general and anthropometrical data: gender, age, age at disease onset, weight and height.

Participants were assessed in two days. On the first day, the clinical parameters were evaluated by an expert physiatrist, by applying the following tests: The Hoehn and Yahr Rating Scale (H&Y) (Hoehn & Yahr, 1967; Goetz *et al.*, 2004) which registered the stage of the disease; the Unified Parkinson’s Disease Rating Scale, the UPDRS (Fahn & Elton, 1987) was used to define the severity of PD. Anxiety levels and symptoms of depression were measured by the Hospital Anxiety and Depression Scale (HAD, Brazilian version; Mondolo *et al.*, 2006), because these are factors that can influence the results of cognitive tests (Garcia *et al.*, 2006; Mantella *et al.*, 2007) (Table 1). Moreover, on the same day, the American Alliance for Health Physical Education Recreation and Dance

(AAHPERD) functional physical ability test was administered to determine patients' physical capacity for participation in the exercise program (Osness *et al.*, 1990) (Table 1).

Executive function and memory results were evaluated on the second day, using the Wisconsin Card Sorting Test (WCST) (Heaton, Chelune, Talley, Kay, & Curtiss, 1993; Paolo, Troster, Axelrod, & Koller, 1995) and subtest Logical Memory I and II from Wechsler Memory Scale – Revised – WMS-R (Wechsler, 1997) respectively. The WCST specifically assesses abstraction, mental flexibility and attention respectively, using the subtests: categories completed, perseverative errors, and failure to maintain set. This test was chosen due to: i) its good construct validity for PD patients; ii) it assesses three executive functions at the same time (abstraction, mental flexibility, and attention) and; iii) it does not require a high level of schooling, which also makes it appropriate for the population involved in our study. To assess the short-term memory (logical memory I) and episodic declarative memory (logical memory II) (WMS-R, Wechsler, 1997), two stories are told separately. Immediately after hearing each story, the patient states what was remembered and the number of linguistic units remembered is computed. After 30 minutes, participants are asked to retell the two stories and the scores for the linguistic units remembered are computed again.

Dependent variables were extracted from the results of the WCST and the WMS-R: abstraction, mental flexibility, attention, short-term memory, and episodic declarative memory, respectively represented by the sum of categories completed, perseverative errors and failure to maintain set (WCST), and number of linguistic units immediately remembered (logical memory I), and after 30 minutes (logical memory II).

### Statistical analysis

Statistical data analysis was performed using SPSS 15.0 software and  $p < .05$  was considered to be significant. To compare the groups (stage of disease and gender) at baseline an independent Student *t*-test was measure. Two ANOVAs

were performed to treat the dependent variables according to the group design. The first two-way ANOVA was performed according to gender, which had group (men and women) and moment (pre- and post-intervention) as factors, with repeated measurement for moment. The second two-way ANOVA was performed according to stage of disease (stage of disease group), which had group (early and moderate stage of PD) and moment (pre and post intervention) as factors, with repeated measurement for moment ( $p \leq .05$ ).

## Results

There were no dropouts during the intervention period and no participant completed less than 70% of the attendance required for data to be included in the analysis. All groups presented similar demographic, clinical and functional characteristics at baseline. There was a gender effect associated with symptoms of depression higher for men than for women (Table 1). In addition, expected differences in clinical aspects (H&Y; UPDRS II and UPDRS III) and in some components of functional capacity (coordination and aerobic resistance) were observed between the stages of disease groups. In this case, patients at early stage of disease had better clinical results and better performance for some functional aspects than patients in later stages of PD (Table 1). No effect from gender or stage of disease on executive functions and memory were observed at baseline (Table 2).

There were main effects from intervention moment in some components of the patients' executive functions and memory. Independent of stage group and gender, positive effect of intervention was observed for abstraction capacities (categories completed:  $F_{1,21} = 8.138$ ;  $p = .01$ ); short-term memory (logical memory I:  $F_{1,21} = 4.891$ ;  $p = .04$ ) and episodic declarative memory (logical memory II:  $F_{1,21} = 18.218$ ;  $p < .001$ ). The statistical analysis didn't show significant interaction between stage of disease groups (early and moderated stages of the disease) and intervention moment (pre- and post-intervention) and, between gender and moment for any of the assessed variables.

Table 2. Means  $\pm$  standard deviations of the dependent variables for each group (gender: man and woman, stage of disease: early and moderated stage). ANOVA *F* and *p* effect values.

Dependents variables	Man		Woman		Effect gender $F_{1,21}$ <i>p</i> values	Early stage of PD		Moderated stage of PD		Effect stage of PD $F_{1,21}$ <i>p</i> values
	Pre-	Post-	Pre-	Post-		Pre-	Post-	Pre-	Post-	
Perserverative Errors (score)	11.0 $\pm 13.5$	6.1 $\pm 9.1$	6.8 $\pm 7.6$	5.6 $\pm 7.7$	.370 .55	5.9 $\pm 6.4$	2.9 $\pm 5.2$	14.8 $\pm 16.0$	11.5 $\pm 10.6$	6.057 .02*
Categories Completed (score)	2.1 $\pm 1.9$	3.1 $\pm 1.9$	2.7 $\pm 1.2$	3.5 $\pm 2.2$	.490 .49	2.9 $\pm 1.6$	4.0 $\pm 1.7$	1.5 $\pm 1.2$	1.9 $\pm 2.1$	6.829 .02*
Failure to Maintain Set (score)	1.0 $\pm 1.3$	1.3 $\pm 1.6$	1.2 $\pm 1.0$	1.1 $\pm 1.1$	.006 .94	1.1 $\pm 1.2$	1.5 $\pm 1.5$	1.0 $\pm 1.1$	0.8 $\pm 1.0$	1.146 .29
Logical memory I (score)	13.5 $\pm 2.8$	16.1 $\pm 5.6$	16.7 $\pm 4.9$	19.0 $\pm 6.3$	2.690 .12	15.5 $\pm 3.6$	19.5 $\pm 5.0$	14.1 $\pm 5.6$	13.8 $\pm 6.6$	3.386 .08
Logical memory II (score)	7.7 $\pm 4.7$	11.2 $\pm 4.2$	11.5 $\pm 5.7$	16.6 $\pm 6.2$	5.247 .03*	10.0 $\pm 5.4$	15.3 $\pm 5.4$	8.5 $\pm 6.2$	10.9 $\pm 6.4$	1.710 .20

NOTE: (\*) Variables that presented significant differences between groups at follow-up.

Independent of intervention moment and PD group, the main effect of gender was observed for memory II ( $F_{1,21} = 5.247$ ;  $p = .03$ ). In this case, the women presented better performance in episodic declarative memory than men (Table 2). There was also a main effect for stage of PD. Independent of intervention moment and gender, patients in the moderate stages of the disease shown significantly lower mental flexibility revealed by perseverative errors ( $F_{1,21} = 6.057$ ;  $p = .023$ ) and abstraction capacity as revealed by categories completed ( $F_{1,21} = 6.829$ ;  $p = .01$ ) than their counterparts in the early stages of the disease (Table 2).

## Discussion

This study investigated the effect of a multimodal exercise program on executive functions and memory in people with PD, taking into account disease severity and gender. Overall, the results showed benefits for PD patients for executive functions and memory after 6 months of exercise intervention, especially in their capacity for abstraction, short-term and episodic declarative memory. Regardless the intervention, the women showed better performance in episodic declarative memory than men, and patients in the moderate stages of the disease scored significantly lower for mental flexibility and abstraction capacity than their counterparts in the early stages of the disease.

The findings also demonstrated that both groups (gender and PD stage groups) were similar in terms of their demographic, clinical, and functional capability characteristics at baseline. Only symptoms of depression were different between genders. Men had significantly higher levels of symptoms of depression than women. In stage of PD groups, the clinical differences observed especially in UPDRS functional and motor subscales were expected. These differences confirm the different stages of disease severity for each group. In addition, the group with moderate disease stage also showed lower performance in coordination and aerobic endurance capabilities. However, this difference in functional capacity didn't prevent the participants at moderate stage of PD from taking part in all proposed activities of the exercise program. We suspect that the diversified activities of the multimodal exercise program were effective in promoting the engagement of these participants in the program. All participants attended the program until the end and they completed 70% or more of the total number of sessions. Some studies report that dropout rate varies from 1 for a 12-week program (Cruise *et al.*, 2010; Lim *et al.*, 2010) to 4 patients in a 6-month program (Allen *et al.*, 2010). In these studies the main reasons for dropouts were due to the health problems that prevented the continuation in the exercise program. In our study, health problems led to absence of the participants in some sessions. However, these absences did not affect the 70% attendance requirement for this study. In addition, we created some strategies to prevent loss of motivation or dropouts caused by difficulty of coming to the place of the interventions. We also used playful activities that increased socialization, and each time the participant missed a session, we called him or her to learn about the reason of the missed session, and to encourage the patient to come to the next session. Furthermore, we provided a

car to transport participants from their homes to the intervention place. These strategies may explain the inexistence of dropouts during the intervention period.

## *Effect of a multimodal physical exercise program*

Since PD is a neurodegenerative and progressive disorder (Olanow, Stern, & Sethi, 2009) it would be expected that after a six-month period these patients would show reduced cognitive performance. Studies have shown that the annual rate of clinical decline in people with PD is between 3.5% (Alves, Wentzel-Larsen, Aarsland, & Larsen, 2005) and 11.2% (García-Ruiz, Meseguer, Del Val, & Vazquez, 2004). However, a positive effect of intervention was observed for abstraction capacities, short-term memory and episodic declarative memory in people with PD.

Reduction in levels of dopamine and acetylcholine are well known to interfere in synaptic plasticity (Calabresi, Picconi, Parnetti, & Filippo, 2006). Some studies showed that 50% of PD patients without dementia exhibited a reduction in acetylcholinesterase, an enzyme precursor of acetylcholine (Calabresi, Picconi, Parnetti, & Filippo, 2006; Perry *et al.*, 1985). These biochemical changes can be directly linked to the causes of dementia in PD (Perry *et al.*, 1985). Our study confirms the results of a previous study that also found improved performance of executive functions in healthy elderly and PD patients after 6 months intervention with physical exercise (Tanaka *et al.*, 2009), and indicates that practicing regular exercise can help the system to compensate for the biochemical and physiological deficits from PD, improving some cognitive functions.

Aarsland *et al.* (2010) observed that in patients with mild cognitive impairment in PD, memory impairment was quite common (13.3%), followed by attention and executive ability impairments (10.1%). To recall information, people with PD can use declarative memory, which requires a conscious effort and attention, or implicit memory (typically unconscious), which is automatically accessed (Johnson, Pollard, Vernon, Tones, & Jog, 2005). People with PD exhibit declarative memory loss, suggesting a problem with memorization strategy (Appollonio *et al.*, 1994). The episodic declarative memory is located in the medial temporal lobe, anterior thalamic nucleus, mammillary bodies, fornix, and prefrontal cortex (Budson & Price, 2005; Robertson, 2002). These structures are affected by the degeneration of dopaminergic and cholinergic neurons in the nigrostriatal pathway in PD, which may explain the impairments in this memory system of PD patients (Calabresi, Picconi, Parnetti, & Filippo, 2006). Thus, the multimodal exercise apparently affected the most impaired memory areas in PD patients.

The benefits of exercise in PD can be associated with the release of neurotropic factors and greater cerebral oxygenation, which together promote new cell growth and cell survival (Fox *et al.*, 2006). Furthermore, in PD, exercise stimulates dopamine synthesis in the remaining intact dopaminergic cells, enhancing the overall operation of the dopamine dependent system (Sutoo & Akiyama, 2003). A recent study suggests five principles of exercise that enhance neuroplasticity in PD: i) synaptic plasticity is maximized by intensive activity; ii) complex activities promote greater structural adaptation; iii) when the activities are rewarding



an increased dopamine levels promote learning/relearning; iv) dopaminergic neurons are highly responsive to exercise and inactivity and v) when exercise is introduced in the early stages of the PD severity progression of the disease likely slows down (Fox *et al.*, 2006). These principles can explain the positive effect of our multimodal physical exercise program and suggest that the intensity and complexity progression of these exercises were appropriate to improve executive functions and memory in PD patients.

### Effect of disease severity

Cognitive impairments are observed in PD patients without dementia, which appear not only in the late stages, but also in the early and moderate stages of the disease (Wu *et al.*, 2012). In our study, we found that the patients in moderate stages of the disease showed deficits in some parameters of executive functions. Lower performance was observed for abstraction and mental flexibility in patients in moderate stage of DP than in patients in early stage of the disease (Perseverative Errors and Categories Completed in Table 2). These results indicate that cognitive impairment, especially in executive functions, tends to progress along with the disease.

Despite the cognitive difference between the early and moderate stages of the disease, both groups took advantage of the multimodal exercises. Interaction between group and moment for any of the variables investigated was not observed.

We can speculate that exercise promotes, at least in part, a protective role against dopaminergic neuronal loss. Therefore, the cognitive gains achieved would minimize losses from disease severity, improving patients' quality of life. Therefore, the multimodal exercise program can play an important tool for preventing cognitive impairment in PD patients.

### Effect of gender

Our results show an effect of gender in the patients' memory performance. In this case, women's episodic declarative memory was significantly better than men's performance. Studies have revealed distinctions between gender with respect to PD (Bower, Maraganore, McDonnell, & Rocca, 2000; Shulman, 2007). Typical symptoms of PD are present in both genders, however, difficulty in writing, trouble in walking and talking are more commonly reported by men, while women more often feel neck and back pain than men (Scott, Borgman, Engler, Johnel, & Aquilonius, 2000). Few studies have attempted to explain these gender differences, especially in relation to cognitive functions. One study that evaluated the prevalence and severity of non-motor symptoms in PD patients by gender showed no differences in memory performance between men and women (Martinez-Martin *et al.*, 2012). These authors observed that fatigue, feelings of nervousness, feelings of sadness, constipation, restless legs, and pain were more common and severe in women. On the other hand, daytime sleepiness, dribbling saliva, interest in sex, and problems having sex were more prevalent and severe in men (Martinez-Martin *et al.*, 2012). In this case, differences among men and women in episodic declarative memory observed

in our study couldn't be supported in the current literature. However, sex hormones are well-established to show neuronal effects, which may differ in men and women. For example, estrogen has different effects on male and female brains (Gillies & McArthur, 2010). These differential effects might potentially influence the clinical differences on non-motor symptoms in male and female PD patients.

Moreover, the presence of more symptoms of depression in men than women, observed in our study, could also explain the difference in memory between the genders. Previous studies have reported that the number of symptoms of depression may predict subsequent memory changes (Gerstorf, Hoppmann, Kadlec, & McArdle, 2009). In this case, there is evidence that depression symptoms account for slower speed of information processing (Landro, Celius, & Sletvoid, 2004), which can affect retention of information and consequently the efficiency of declarative memory.

### Study limitations

The limitations of our study are the small sample size and the lack of a control group. The inclusion of a control group (untreated patients) in future studies could provide answers about the evolution of cognitive impairment in men and women with PD. Thus, the proportions of the cognitive gains with the physical training could be better understood.

### Conclusion

Overall, although PD is a neurodegenerative and progressive disorder, these preliminary results showed that the multimodal exercise program is effective in maintaining cognitive functions in PD patients. Furthermore, exercise seems effective in improving patients' memory and some domains of executive function. Cognitive functions decrease with disease severity. However, regardless of gender and disease severity, multimodal exercise was effective in improving these functions, suggesting that exercise can be prescribed as a preventive strategy to mitigate progressive cognitive deficits in the later stages of the disease.

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